Main Group Metals in Organic Synthesis

Edited by
Hisashi Yamamoto and Koichiro Oshima

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Contents

Volume 2

Preface

Historically, main-group organometallics and metallorganics have played a major role in modern organic synthesis. The Grignard reagent has played quite a significant role in this field of chemistry for more than one hundred years. For most chemists, this type of magnesium compound is probably the first organometallic reagent that is encountered in their first organic-chemistry course. Although the use of Grignard reagents is truly impressive, the actual mechanistic details of reactions of these well-known organometallic compounds are still vague. Recent advances in various analytical technologies have allowed us to understand some of details of reactions that use the classical reagent. In light of the elucidation of various mechanisms, we now recognize the role of Grignard reagents in organic synthesis to be even greater than first anticipated.

Now that we are able to understand the chemical behavior of many main-group elements such as lithium, silicon, boron, and aluminum, the purpose of this book is to summarize these recent developments and show the promising future roles of complexes of these metals in modern organic synthesis. In fact, these reagents are both useful and much safer than most transition-metal compounds.

This volume focuses on areas of main-group organometallic and metallorganic reagents selected for their significant development during the last decade. Each author is very knowledgeable in their particular field of chemistry, and is able to provide a valuable perspective from a synthetic point of view. We are grateful to the distinguished chemists for their willingness to devote their time and effort to provide us with these valuable contributions.

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1
Lithium in Organic Synthesis

Katsuhiko Tomooka and Masato Ito

1.1
Introduction

Organolithium compounds are central to many aspects of synthetic organic chemistry and are primarily used as carbanions to construct carbon skeletons of a wide variety of organic compounds. Despite the strictly anhydrous conditions generally required for successful performance of reactions using organolithium compounds, their fundamental significance in synthetic organic chemistry remains unchanged. Tremendous efforts have therefore been devoted to the development of convenient methods for generation of tailor-made organolithium compounds and useful reactions using conventional organolithium compounds.

Because comprehensive literature [1–8] covering various aspects of organolithium chemistry has recently become available, the purpose of this chapter is to highlight "powerful synthetic tools" involving organolithium compounds. The definition of "organolithium" is here limited to those compounds in which there is a clear C–Li bond; compounds with enolate or ynolate structures or with heteroatom (Y)–Li bonds, etc., have been excluded.

This chapter is roughly divided into three sections. The nature of organolithium compounds, their structures, the configurational stability of their C–Li bond, and general guidelines regarding the handling organolithium compounds are briefly considered first (Section 1.2). The next section concerns the classification of useful methods for generation of organolithium compounds in which new C–Li bonds are created either by reduction, using lithium metal itself, or by the conversion of a C–Li bond into a less reactive C–Li bond (Section 1.3). The last section primarily describes potential methods for construction of the carbon framework, driven by conversion of a C–Li bond into a less reactive Y–Li bond (Section 1.4). All the examples dealt with in the last two sections have been selected on the basis of the distinct advantages of employing organolithium compounds compared with other organometallic reagents. We will not detail pioneering works underlying the establishment of selected examples, because we are concerned that excessive comprehensiveness might obscure their marked synthetic importance. There is no doubt, however, that modern synthetic technology has been developed on the basis of the considerable efforts of our forefathers, and readers are strongly recommended to

refer to other books or reviews cited in this chapter for historical aspects and other issues regarding organolithium chemistry.

1.2
Nature of Organolithium Compounds

1.2.1
Overview

Because organolithium compounds are generally sensitive to oxygen and moisture, rigorous exclusion is required to prevent decomposition. They are, however, stable in anhydrous hydrocarbons under a nitrogen or, preferably, argon atmosphere at ambient temperature, and the solutions can be stored for longer at low-

Tab. 1.1 Commercially available organolithium compounds

Organolithium compound	Abbreviation	Solvent	Concn (M)
Methyllithium	MeLi	Diethyl ether	1.0[a]
			1.4[c]
Methyllithium-lithium bromide complex	MeLi–LiBr	Diethyl ether	1.5[c]
			2.2[b]
Methyllithium-lithium iodide complex	MeLi–LiI	Diethyl ether	1.0[c]
n-Butyllithium	*n*-BuLi	Hexane	1.6[a–c]
			2.5[b, c]
			2.6[a]
			3.0[a]
			10.0[c]
		Cyclohexane	2.0[c]
		Pentane	2.0[c]
s-Butyllithium	*s*-BuLi	Cyclohexane	1.0[a]
			1.3[c]
			1.4[b]
t-Butyllithium	*t*-BuLi	Pentane	1.5[a]
			1.7[c]
Phenyllithium	PhLi	Cyclohexane-diethyl ether	1.0[a]
			1.8[c]
			1.9[b]
		Dibutyl ether	2.0[b]
Lithium acetylide-ethylene-diamine complex	$HC \equiv CLi–H_2NC_2H_4NH_2$	None (powder ca. 90% purity)	_[a–c]
		Toluene (suspension 25%, *w/w*)	_[b,c]

a) Kanto Kagaku. **b)** Wako Chemicals. **c)** Sigma-Aldrich.

er temperatures [1, 2]. Simple organolithium starting materials listed in Tab. 1.1 are commercially available as solutions in such solvents. Exceptionally, the lithium acetylide-ethylenediamine complex is available as a solid. Hydrocarbon solutions of n-, s-, and t-BuLi are the ultimate source of most organolithium compounds, and their availability has greatly contributed to the advancement of organolithium chemistry. In general, ethereal solvents such as diethyl ether or tetrahydrofuran are most frequently used either in the preparation of organolithium compounds or in their reactions, because they reduce the extent of aggregation of organolithium compounds and hence increase their reactivity (Section 1.2.2). To increase their reactivity further, N,N,N',N'-tetramethylethylenediamine (TMEDA), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidine (DMPU), or hexamethylphosphoramide (HMPA) are effective co-solvents, because of their high coordinating ability. It should be noted that organolithium compounds are thermally unstable in ethereal solvents; their half-lives [1, 9, 10] are summarized in Tab. 1.2. Thermal decomposition arises as a result of deprotonation of ethereal solvents by organo-

Tab. 1.2 Half-lives of organolithium compounds in common ethereal solvents

RLi	Solvent	−70°C	−40°C	−20°C	0°C	+20°C	+35°C
t-BuLi	DME	11 min					
	THF		5.6 h	42 min			
	ether			8 h	1.0 h		
s-BuLi	DME	2.0 h	2 min				
	THF			1.3 h			
	ether			20 h	2.3 h		
n-BuLi	DME			1.8 h	<5 min		
	THF				17 h	1.8 h	10 min
	ether					153 h	31 h
PhLi	ether						12 days
MeLi	ether					3 months	
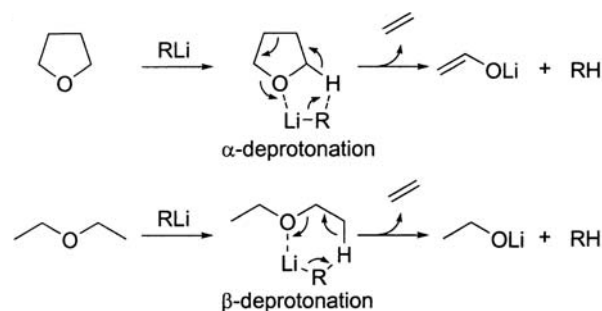
Scheme 1.1

lithium compounds, because of their high basicity, leading to a variety of decomposition products with Li–O bonds, as illustrated in Scheme 1.1.

1.2.2
Structural Features

The electron-deficient lithium atom of an organolithium compound requires greater stabilization than can be provided by a single carbanionic ligand, and freezing measurements indicate that in hydrocarbon solution organolithium compounds are invariably aggregated as hexamers, tetramers, or dimers [11] (Tab. 1.3). The structures of these aggregates in solution can be deduced to some extent from the crystal structures of organolithium compounds [12] or by calculation [13]: the tetramers approximate to lithium atom tetrahedra unsymmetrically bridged by the organic ligands [4, 5]. The aggregation state of simple, unfunctionalized organolithium compounds depends primarily on steric hindrance. Primary organolithium compounds are hexamers in hydrocarbons, except when branching β to the lithium atom leads to tetramers. Secondary and tertiary organolithium compounds are tetramers whereas benzyllithium and very bulky alkyllithium compounds are dimers [1, 11].

Coordinating ligands such as ethers or amines, or even metal alkoxides can provide an alternative source of electron density for the electron-deficient lithium atoms. These ligands can stabilize the aggregates by coordinating to the lithium atoms at their vertices; this enables the organolithium compounds to shift to an entropically favored lower degree of aggregation. As shown in Tab. 1.3, the presence of ethereal solvents typically causes a shift down in the aggregation state, but only occasionally results in complete deaggregation to the monomer [1]. Methyllithium and butyllithium remain tetramers in diethyl ether, THF, or DME, with some dimers forming at low temperatures; *t*-BuLi becomes dimeric in diethyl

Tab. 1.3 Aggregation states of typical organolithium compounds

RLi	*In hydrocarbon solvent*	*In ethereal solvent*
MeLi	–	Tetramer
EtLi	Hexamer	Tetramer
n-BuLi	Hexamer	Tetramer
i-BuLi	Tetramer	–
BnLi	Dimer	Monomer
i-PrLi	Tetramer	Dimer
s-BuLi	–	Dimer
PhLi	–	Dimer
t-BuLi	Tetramer	Dimer

ether and monomeric in THF at low temperatures [14–17]. Coordinating solvents also greatly increase the reactivity of the organolithium compounds, and an ether or amine solvent is indispensable in almost all organolithium reactions.

1.2.3
Configurational Stability

In principle, the configurational stability at the metal-bearing stereogenic carbon in organometallic compounds decreases as the ionic character of the carbon–metal bond increases. Because organolithium compounds contain one of the most electropositive elements some charge separation occurs in their C–Li bonds. Coordinating solvents greatly enhance the extent of charge separation. Enantio-enriched organolithium compounds, if successfully generated, usually, therefore, undergo racemization, which can be explained by migration of the Li cation from one face of the anion to the other. For example, the half-lives for racemization of secondary, unfunctionalized organolithium compounds in diethyl ether are only seconds at $-70\,^{\circ}$C, even though those in non-polar solvents can be lengthened to hours at $-40\,^{\circ}$C and to minutes at $0\,^{\circ}$C [18]. Accordingly, the design of stereoselective reactions with enantio-enriched organolithium compounds has long been unattractive to the synthetic organic community. The last decade, however, has witnessed a significant advance in this area, and a number of functionalized organolithium compounds with a configurationally stable C–Li bond have been found by taking advantage of the Hoffmann test [19], which provides a qualitative guide to the configurational stability of an organolithium compound.

The Hoffmann test, the essence of which is described briefly below, comprises of two experiments using a suitable chiral electrophile such as an aldehyde in either the racemic or enantiomerically pure form. The occurrence of sufficient kinetic resolution on reaction of a racemic organolithium compound (±)-**1** with a chiral electrophile **2** is established in the first experiment by using **2** in the racemic form. In a second experiment the organolithium compound (±)-**1** is added to the enantiomerically pure **2** and the ratios (a and a') of the diastereomeric products **3** and **4** resulting from the two experiments are compared. If they are identical ($a = a'$) at conversions of >50%, the organolithium compound **1** is configurationally labile on the time-scale set by the rate of its addition to **2**. If there is an analytically significant difference between the diastereomer ratios ($a \neq a'$), enantiomer equilibration of the organolithium compound is slower than its addition to the electrophile (Chart 1.1).

experiment I

(±)-**1**   (±)-**2**   (±)-**3**   (±)-**4**

diastereomer ratio a = (±)-**3**/(±)-**4**
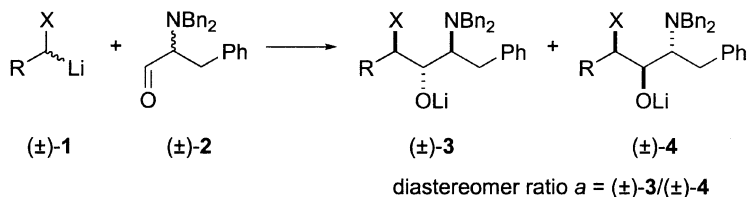
If a = 1, test is insensitive.
If $a \neq 1$, go to Experiment II.

experiment II

(±)-**1**   **2**   **3**   **4**

diastereomer ratio a' = **3**/**4**
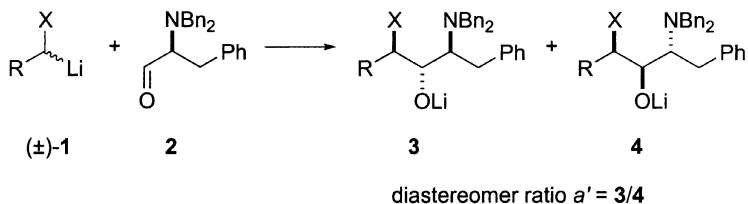
If a' = a, **1** is configurationally *unstable*.
If $a' \neq a$, **1** is configurationally *stable*.
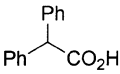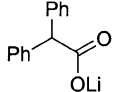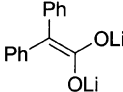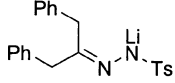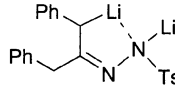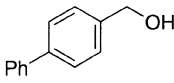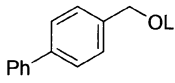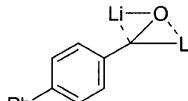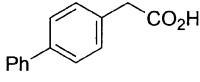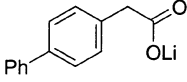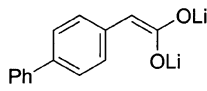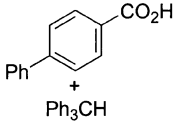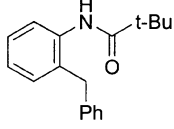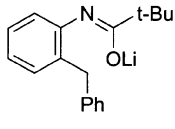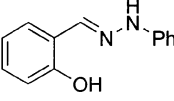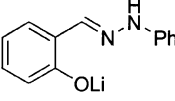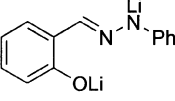
Chart 1.1   The Hoffmann test

1.2.4
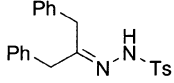### Titration of Organolithium Compounds

One can easily and reliably check the identity, purity, and concentration of an organolithium compound in solution by several methods. One of the most standard methods is titration of the organolithium solution with alcohols such as 2-butanol (**5**) or (–)-menthol (**6**) in the presence of a small amount of 2,2′-bipyridine (**7**) or 1,10-phenanthroline (**8**) as a color indicator. This method is based on the color difference between the C–Li and O–Li compounds, with the ligands used as color indicators (Scheme 1.2). For example, addition of a spatula tip of **8** to a solution of an organolithium species in an ether or a hydrocarbon produces a characteristic rust-red charge-transfer (CT) complex. Titration with a standardized solution of **5** in xylene until complete decoloration enables determination of the concentration of the organolithium compound [20]. To minimize the experimental complexity a variety of indicators [21–25] bearing a functional group to coordinate to lithium and another to develop a color within the same molecule have been developed, as shown in Tab. 1.4. However, one should select appropr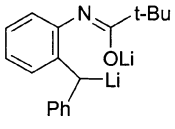iate color indicators depending on the structure of the organolithium compounds that correlate with the sharpness of color development.

Tab. 1.4 Color indicators in titration

Color indicator	Color change		Suitable RLi	Refer-ence
	colorless	yellow	MeLi n-BuLi	[21]
	colorless	orange	MeLi n-BuLi t-BuLi PhLi	[22]
	colorless	orange red	MeLi n-BuLi s-BuLi t-BuLi	[23]
	colorless	bright yellow	n-BuLi s-BuLi t-BuLi	[23]
+ Ph₃CH	colorless	deep red	n-BuLi s-BuLi t-BuLi	[23]
	colorless	yellow orange	MeLi n-BuLi s-BuLi t-BuLi PhLi	[24]
	yellow	red	MeLi n-BuLi t-BuLi	[25]

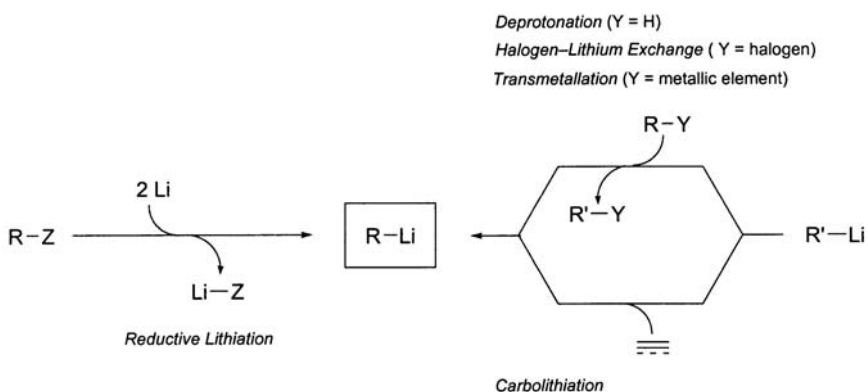R'OH : **5**   **6**   N   N : **7**   **8**
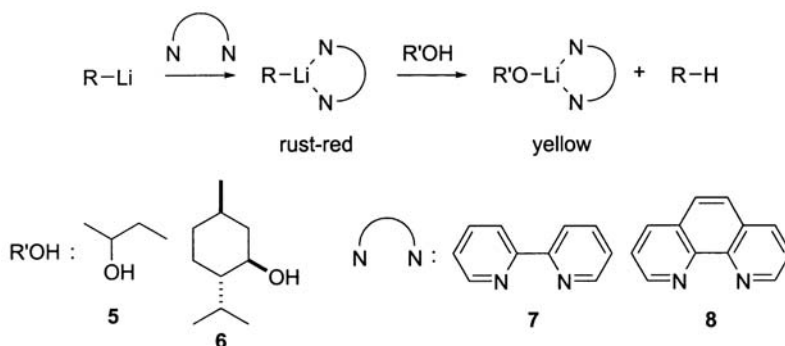
Scheme 1.2

1.3
Methods for the Preparation of Organolithium Compounds

1.3.1
Overview

A C–Li bond can be created by one of two principally different methods. One is the de novo creation of C–Li bonds in which the lithium metal undergoes reductive insertion to an organic compound with the leaving group Z; the other involves construction of new C–Li bonds by another organolithium reagent (Scheme 1.3). The former method, detailed in Section 1.3.2, is still the most straightforward and often also the most rational approach; it is therefore used in the industrial production of typical organolithium compounds. The latter method

Deprotonation (Y = H)
Halogen–Lithium Exchange (Y = halogen)
Transmetallation (Y = metallic element)

R–Z   2 Li   R–Li   R–Y   R'–Y   R'–Li

Li–Z

Reductive Lithiation

Carbolithiation

Scheme 1.3